U. S. ARMY MEDICAL RESEARCH & NUTRITION LABORATORY

REVIEW OF THE UNITED STATES ARMY'S IRRADIATED FOOD WHOLESOMENESS PROGRAM

REPORT 268
29 MAY 1962

UNITED STATES ARMY
MEDICAL RESEARCH AND DEVELOPMENT COMMAND

U. S. ARMY MEDICAL RESEARCH AND NUTRITION LABORATORY
FITZSIMONS GENERAL HOSPITAL
Denver 30, Colorado

Report No. 268 29 May 1962

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By

M. E. McDOWELL
and
N. Raica, Jr.

REVIEW OF THE U. S. ARMY'S IRRADIATED FOOD
WHOLESOMENESS PROGRAM

Marion E. McDowell, Lt. Colonel, MC, U. S. Army
and
Nicholas Raica, Jr., Ph.D.

Presented, in part, by Lt. Colonel McDowell at the FAO/WHO/IAEC Technical Meeting on the Evaluation of Wholesomeness of Irradiated Foods. Brussels, Belgium, 23 - 30 October 1961*

In the United States the Army's Quartermaster Corps has conducted extensive research into the feasibility of preserving food by the use of ionizing radiation. Knowledge of the wholesomeness of food, so preserved, is of major importance to the achievement of this goal. Responsibility for testing irradiated food wholesomeness was given to The Surgeon General, U. S. Army, and a research program thereon was initiated in 1953. This has since been in progress through work done in the medical laboratories of the Army Medical Service, and in civilian academic and research institutions through contracts and grants monitored by the Medical Research and Development Command of the Army Surgeon General.

* Subsequently the list of references has been extended, and updated to include the scientific literature publication of some material previously available only in official report form.

In June of this year (1961) a meeting of contractors and in-service investigators was held in Chicago, under the auspices of the Quartermaster Corps, the Quartermaster Food and Container Institute for the Armed Forces, and the Medical Department, U. S. Army, for the purpose of reviewing the progress made in all aspects of the Army Radiation Preservation of Foods Project. This meeting included a section devoted exclusively to summary reports from investigators studying wholesomeness problems. My present report will draw heavily from information presented at the meeting (1), as well as from published reports, and will attempt to summarize and interpret the current status of the testing program on wholesomeness. Since similar interim reports have been presented to previous international meetings such as this there will necessarily be some repetition. However, it seems desirable to spend some time in reviewing the overall results, even if repetitive, in order that the remaining problems be not falsely over-emphasized.

Wholesomeness involves two areas, nutritive value and toxicity (not always easily separated). However, it would seem that the area of toxicity testing deserves the most emphasis in the present discussion. While it is extremely important to know the nutritive losses produced in the irradiation process, these losses, when quantitated, can presumably be easily corrected by appropriate fortification of the diet and/or combinations of a variety of foods. (Other speakers have already initiated discussion of these areas).

In the toxicity studies (2,3), experimental animals have been given a diet containing the irradiated food in quantity greater than that food would ordinarily be consumed, in order to maximize expression of any potential toxicity. In addition, such diets contain adequate quantities of all nutrients (provided by supplementation with non-irradiated food, and/or vitamin-mineral mixtures) known to be required for proper growth and development. Individual irradiated food items have usually been incorporated into the total diet at a level of 35% of the dry solids. Two levels of irradiation (2.79 and 5.58 megarads) have usually been tested in comparison with a non-irradiated control. Certain foods such as potatoes, oranges, and flour have had appropriately lower radiation dosage. Initial experiments utilized short term rat feeding studies of from 8 - 12 weeks duration which served to clear a large number of foods for brief human taste panel (or palatability) evaluation (4-9).

This paper will focus attention on the more significant chronic toxicity experiments which have since been conducted using 2 year feeding tests in rats and in dogs. In addition, one group of investigators has performed the long term tests using monkeys. Several groups, particularly those investigating carcinogenicity, have conducted studies using several strains of mice. In long term studies in rats (2), parent replicates were fed the experimental and control diets for 2 years, or for their life

span if less than 2 years. After 12 weeks of feeding after weaning, males and females were randomly selected within each feeding group, and mated. The first litters were raised to weaning, weights and mortality were recorded, and the weanling survivors were then discarded. The parent generation animals were then remated using different males, but within the same feeding groups. The same weaning and weight gain data were recorded for their second litters. (The parent generation continued on feeding and observation for their life span or 2 years.) Animals from these second litters were fed the same foods as their parents, by group, for 100 days and were then used to reproduce the 3rd generation, staying on the diets through weaning of the second litters. Again, growth and weaning data were kept on 1st and 2nd litters, but only 2nd litters were placed on the same feeding program as their parents, and used to obtain the 4th generation. The 2nd litters of the 4th generation were raised to weaning. Thus, these "two year - four generation" studies permitted an evaluation of reproductivity, lactation, longevity and early genetic effects as well as the usual measurements of growth or maintenance of weight, feed efficiency and food consumption, incidences of various diseases, laboratory signs of toxicity as revealed by hematologic and renal function tests, blood chemistry, etc., and pathology, both gross and microscopic. Studies performed in the dog should ideally have a much longer period than two years to obtain life span data, but for practical considerations, a two year feeding period has

been accepted (3). Except for a few foods such as potatoes, cabbage, and oranges, the irradiated foods used had been stored, after irradiation, at room temperature for at least 3 months prior to feeding.

A logical, yet simple, organization of all these studies is difficult because of the wide varieties of diets and species used, as well as the differences in the stage of completion of experiments, and parameters measured. In addition, as certain findings have emerged, new special studies have been set up to test these more completely. Some investigators studied each irradiated food separately, while others, utilizing a factorial design, tested 2 irradiated items together. This was possible by feeding the 2 foods in all nine possible diet combinations of the non-irradiated, 2.79 megarads irradiated, and 5.58 megarads irradiated items. The latter method was economical of animals, and also permitted evaluation of possible interaction between 2 irradiated foods in the diet.

Each food item will be discussed separately though simultaneous testing of 2 foods will be mentioned where applicable. For brevity, negative findings will not always be cited, and omission of mention does not mean that the observation was not made. When the observation was not carried out, or remains to be evaluated, and when irradiated food appears to be associated with an unusual result, then the specific parameter will be noted. Some of the studies have

yet to be completed and many studies lack the histopathology review of tissues being conducted by the Armed Forces Institute of Pathology in Washington (10-12). The first group of foods (table 1) to be considered are those receiving relatively low dosage of irradiation; potatoes, flour, and oranges. Brownell, et al, (13) at the University of Michigan, fed a diet containing irradiated potatoes to rats for up to 2 years. Two levels of sprout-inhibiting dose ranges were tested: 13 - 20 and 27 - 40 kilorads. No consistent effects due to irradiation of potatoes could be established. However, there was a slightly greater mortality rate among males of the 1st generation fed the irradiated diets. This was of questionable statistical significance and may have been related to the poor condition (i.e. slight decay) of the irradiated potatoes relative to the non-irradiated controls. Second generation males and females fed the irradiated potato diets also experienced a higher mortality rate but this was attributed to genetic factors unrelated to the feeding of irradiated food. Shortly thereafter, another group of investigators, Kline (14,15), et al, at the Wisconsin Alumni Research Foundation performed similar experiments but used potatoes irradiated at lower dosages (7,500 - 8,500 rads and 15,000 - 17,000 rads). Sprouting was controlled but there was much less trouble with the spots of decay that the other potatoes had developed. Careful statistical analysis indicated no toxic effects which could be ascribed to the irradiation treatment. The growth, fertility, longevity, blood

picture, and pathology, including cancer incidence, was practically identical in all groups. McCay and Rumsey (16), of Cornell University, have also completed a 2 year feeding test in 12 dogs (beagles). Eight of them ate an irradiated potato diet (35% of solids of the diet); 7,000 and 15,000 rads were used. Although this diet was supplemented with vitamins and liver, it did not prove to be a nutritious diet as judged by the poor reproduction and growth of the dogs. However, the poor record of reproduction and growth were evident in the control diet as well. One can conclude that the higher level of irradiation increases decay of potatoes, but that at the 8 - 15 kilorad level there are no adverse effects when fed to rats. In addition, it appears that a 35% potato diet is not optimum for dogs, but irradiation of the potatoes, per se, does not seem harmful.

Tinsley, et al (17), at Oregon State University, conducted long term rat feeding experiments using flour irradiated at 37 and 74 kilorads for the purpose of reducing insect infestation. No statistically significant treatment effects were observed in these experiments. The final microscopic examinations of tissues from these animals have not been completed. Reber, et al (18,19), at the University of Illinois, College of Veterinary Medicine, have completed a long term study in dogs using flour irradiated at the aforementioned levels. Results indicated that feeding irradiated flour to dogs had no significant detrimental effects on growth,

feed conversion, hematologic values, fertility or lactation as compared to dogs fed non-irradiated flour. Thyroid changes, primarily that of a subacute to chronic thyroiditis with atrophic acini, appeared to increase with the increasing irradiation feeding level, but the number of cases were too few to be statistically significant. Flour, irradiated at approximately 80 kilorads, is one ingredient in a composite diet being fed to mice by Calandra and Kay (20) at the Industrial Bio-Test Laboratories, Illinois, in a carcinogenicity experiment, with no significant differences as yet noted between control and test mice with regard to growth patterns or mortality. Final data on growth and tumors are not yet available.

Long term rat feeding experiments on oranges have been conducted by Phillips, et al (21), Syracuse University. Whole oranges were exposed to 0.14 and 0.28 megarads of electron beams in order to increase the refrigerated shelf life. They were peeled before feeding. Non-irradiated oranges and those irradiated at two levels were fed along with shrimp, also non-irradiated and irradiated at two levels, in the nine possible combinations. No differences between controls and the irradiated food groups could be detected at a statistically significant level. This is in contrast to the similar study conducted by the same group when the irradiated whole oranges were fed without peeling (22). In this case, the third generation animals showed significantly lower weight gains in the irradiated diet groups than shown in the

corresponding controls. Statistical evaluation of food consumption and initial weight data failed to indicate a basis for the differences noted in growth rate. While irradiated oranges had no apparent effect on growth of the parent generation rats and their offspring, the growth of rats in the subsequent (third) generation appeared to be influenced by the irradiated component in the diet. In both of these studies, several enzyme activities were measured in the duodenum and the intestinal mucosa in rats fed the diet for 19 to 20 days and for approximately 200 days. In the irradiated whole orange group there were rather marked increases in duodenal enzymes, observed particularly in female rats, especially with regard to the activities of glutamic oxalacetic transaminase, glutamic pyruvic transaminase and monoamine oxidase. In the peeled orange and shrimp diet groups, the only enzyme abnormality was an elevated duodenal sucrase activity in weanling rats fed the irradiated diet for 20 days. This effect on sucrase was not observed in rats fed the irradiated diet for 36 weeks. Blood and Darby (23), at Vanderbilt University School of Medicine, are the only investigators who have used monkeys as experimental animals in the irradiated food program. In a two year study, eight monkeys were fed whole irradiated oranges and another eight received irradiated oranges which had been peeled. Growth data were difficult to interpret because of a variation in food habits of individual animals. It was generally concluded however, that the growth was satisfactory considering all variables present, and

that no consistent differences attributable to the irradiation could be detected.

The next foods to be discussed have been irradiated at the higher levels, 2.79 and 5.58 megarads (table 2). A number of investigators have studied beef. Blood and Darby (24,25), in a long term four generation study in rats, reported that all animals appeared to grow satisfactorily and there was no undue mortality in any of the groups. Hematologic studies were normal throughout and no hemorrhagic syndrome was observed. There was no evidence that reproduction was impaired due to the feeding of irradiated foods. Most of the male and female rats were fertile and could produce more than one litter of young. McCay and Rumsey (26) extended the long term study of ground beef to dogs, their three year experiment ending in 1958. The hematological and growth data did not indicate any detrimental effects from the feeding of irradiated beef. However, in the reproductive studies the number of conceptions were reduced in both irradiated food groups and the number of pups whelped and the number of pups weaned were fewer as the irradiation level of the dietary beef increased. Because it appeared that vitamin E in the ration was submarginal, a repeat experiment has been undertaken in the same laboratory. Thirty-six registered purebred beagles between 8 and 10 weeks of age were started on experiments soon after weaning in September 1960. Electron irradiated beef at 5.58 megarads is being used. Vitamin supplements in this experiment include 400 units of vitamin E

weekly, as opposed to two units monthly in the preceeding experiment. At eight months along in the 3 year experiment the growth curves for both dietary groups were reported to be normal and similar, and the dogs were said to be growing and maturing faster than usual as compared with the kennel norm. However, this study cannot be finally evaluated until 1963. Reber, et al (27,28), at the University of Illinois College of Veterinary Medicine, have also studied the effects of feeding irradiated beef to dogs for two years. No gross abnormalities or ill effects were observed. However, there was a significant decrease in food consumption during the initial 24 week growth period in dogs fed the 5.58 megarad irradiated beef, but no significant differences were noted in efficiency of feed conversion or overall weight gains. It was concluded that feeding irradiated beef to dogs had no significant effect on the growth, feed conversion, fertility, or lactation as compared to dogs fed non-irradiated beef. There were no apparent adverse hematological effects. Histopathological examination of tissues revealed no consistent lesions that could be associated with the feeding program. Clarkson and Moreland (29) at Bowman Gray School of Medicine have set out to repeat the reproductive performance study in beagle dogs initiated by McCay and Rumsey (26). Three males and 15 females receiving irradiated beef (5.58 megarads) will be compared with a similar control group eating non-irradiated beef. The experiment will not be completed until the fall of 1962, however, at 10 months no significant differences had been detected.

Since reproduction is the main interest of this study, both the control and irradiated beef, as well as each lot of dog food used as the balance of the diet, will be assayed for estrogenic substances.

Deichmann (30), of the University of Miami School of Medicine, has completed a two year, four generation study of beef stew (C ration) fed to rats. No significant differences were observed between control and experimental groups but the histological examination of the tissues has yet to be completed. Beef, and beef stew, as components of composite diets or mixed diets will be reported later, as well as the role of beef in the hemorrhagic syndrome in rats.

Irradiated pork has been studied by Tinsley (17), et al, using long term rat tests. The only significant differences between controls and irradiated pork-fed rats occurred in the decreased weaning efficiency of animals fed the 2.79 megarad pork ration. Examination of the data shows that this was due to a low figure in the parent generation and that it did not appear in subsequent generations. Furthermore, since it did not occur at the higher irradiation level it is not considered to be of biological significance. Preliminary histopathological data does not suggest any unfavorable effect of irradiated food but the data remains to be reviewed (31). In a long term study using dogs, McCay and Rumsey (26) found no deviations from the normals in the irradiated pork fed group.

Irradiated boned chicken was studied by Blood and Darby (25) who found no differences in dogs fed irradiated and non-irradiated chicken for two years. A long term, four generation rat study has been conducted by Richardson (32), at the Texas Agricultural Experiment Station, who tested chicken, fed with green beans, according to the factorial design previously mentioned. Again, no significant differences in weight gain, hematology, reproductive abnormalities, or incidences of gross and histopathologic abnormalities occurred which could be attributed to the irradiated food.

Chicken stew as used in the Army "C ration" has been studied by two groups of investigators. Phillips, et al (33), at Syracuse University, have fed chicken stew in combination with raw shredded cabbage in a two year, four generation rat study. The control animals and the irradiated diet animals were generally comparable. Histopathologic data is yet to be reported. McCay and Rumsey (26) found that their dogs readily ate an irradiated chicken stew diet for two years, and showed normal growth, hematology and no differences from dogs on the non-irradiated chicken stew diet.

Three seafoods have had long term tests (table 2): codfish, tuna fish, and shrimp. Using both rats and dogs, Alexander and Salmon (34) and Newberne (35,36) of Auburn University, found no unfavorable effects, including histopathology, due to irradiation of codfish. Tuna fish was fed by McCay, et al (26), in a long

term dog study which revealed no differences between control groups and irradiated tuna fish groups. The reproduction data are too few to yield any conclusions, and the histopathology data have yet to be reported. Paynter (37), of the Hazleton Laboratories, Falls Church, Virginia, fed irradiated tuna fish in combination with irradiated corn in a long term rat study including a two generation reproduction study. There were no significant differences noted between controls and those fed irradiated food. Shrimp has been fed by two groups. As mentioned before, Phillips, et al (21), conducted a long term rat feeding study using nine combinations of irradiated and non-irradiated shrimp and irradiated and non-irradiated oranges. No untoward effects of irradiation were noted. Engel, et al (38,39), of Virginia Polytechnic Institute, observed no untoward effects from feeding irradiated shrimp to dogs. Further studies have shown that in dogs fed irradiated shrimp there is no difference from the control group in the serum antibody response to certain test antigens. Also, there were no differences in serum non-protein nitrogen, chlorides, albumin, globulin, or gamma globulin.

Blood and Darby (23) fed irradiated peaches (table 3) to eight monkeys for two years. No abnormalities attributed to toxicity of the irradiated food were observed although it was necessary to supplement the diet with ascorbic acid when the monkeys on irradiated peaches failed to eat all of the ration. Fifty mgm of ascorbic acid

daily apparently corrected this abnormality. In a long term rat experiment, Tinsley, et al (17), found no significant abnormalities associated with the feeding of irradiated peaches. Mead and Griffith (40), at the University of California, Los Angeles, fed nine combinations of irradiated and non-irradiated bacon and fruit compote in a two year - four generation rat study. They state "There appears to be a small longevity factor in favor of the control diet". Inspection of these data shows the differences to be very small and apparently of no biological significance. Further statistical analysis of these data is needed. In all other respects there were no differences between experimental and control groups. Larson, et al (41), of the Medical College of Virginia fed irradiated fruit compote to pure-bred beagle dogs for a period of two years. No effects attributable to irradiated food were apparent as regards growth, food efficiency, reproduction, hematology or histopathology. A possible exception, of unknown biological significance, was a trend toward increased spleen weights in animals receiving the irradiated food.

Canned pineapple jam irradiated at two levels, and non-irradiated jam, were fed by Blood and Darby (25) to dogs for a two-year study. While growth was erratic with all animals, no correlation could be made between the type of diet and the growth response. All animals receiving the jam showed glycosuria on most tests. This was attributed to the high carbohydrate content of the diet and was verified by quantitative determinations of the

fasting blood sugar level. All animals approached a normal value after a 24-hour fasting period. Reproduction was very poor in all animals but with no significant differences due to irradiation of the food. Tinsley, et al (17), found no differences between control and irradiated jam diets in their long term study using rats.

Proctor, et al (42), at Massachusetts Institute of Technology, (table 3) fed rats irradiated dried whole eggs for a two-year study. In general, no significant differences between the various experimental groups in any of the determinations were observed. Tissues taken at periodic intervals throughout the test revealed no evidence of any pathological process which could be attributed to the feeding of irradiated eggs. Similar results were obtained during a chronic study with dogs extending over four years, except for poor reproductive performance, which was thought to be related to the avidin content of the uncooked eggs. There was slight evidence that biotin supplementation of the diet in the latter half of the experiment may have been responsible for the improvement in reproductive performance.

Deichmann (43), University of Miami School of Medicine, has studied irradiated canned evaporated milk in long term experiments in both rats and dogs. Studies have been completed in the rat and show no unfavorable effects due to irradiation of the milk. Histologic study of the tissues of the dogs remains to be accomplished.

Five vegetables have been studied in long term experiments (table 4). Engel (38,39), at V.P.I. found no unfavorable effects in feeding carrots to dogs. However, Tinsley, et al (17), have reported that rats raised on the irradiated carrot ration showed a lower rate of growth than those on the control carrot ration. This effect was more pronounced in the male animal. Although the decrease was small it was consistent and cannot be explained by differences in food intakes. The possibility of some bacterial contamination in the irradiated carrots has not been definitely eliminated. Further experiments are underway to check this finding and, if repeated, to define the nature of the defect. There was no difference in the growth rates between the two levels of irradiation. All other measurements showed no effect attributable to irradiation. As mentioned previously, green beans were studied by Richardson (32), who conducted a long term rat feeding experiment using nine different combinations of green beans and chicken. No abnormalities due to the irradiation were found. Larson, et al (41), fed green beans to dogs and noted no differences due to irradiation except for a trend to increase in spleen weights in the 5.58 megarads group. A two-year feeding study of irradiated cabbage in dogs performed by Hale and associates (44) at the Georgia Coastal Plain Experiment Station revealed no abnormalities. Phillips and others (33) found no consistent significant abnormalities in their long term study in rats fed nine different combinations of cabbage and chicken stew. In a two-year study,

McCay (45) found that irradiated canned corn fed to dogs produced no deviations from the normal, although the reproduction data on the females were too few to evaluate satisfactorily (table 4). Corn was also fed to rats by Paynter (37), Hazleton Laboratories, along with tuna fish and no untoward effects found. Sweet potatoes have been fed by Alexander and Salmon (34), and Newberne (35,36), in long term experiments in both rats and dogs. The rats received nine combinations of sweet potatoes with codfish while the dogs received sweet potatoes separately. Reproduction was poor in control and treatment groups in both species but all other parameters, including histopathology, revealed no differences due to the irradiation of the food.

The last food (table 4) to be discussed in this section is irradiated bacon. A petition is being prepared by the Quartermaster to the Food and Drug Administration requesting its clearance for human feeding. Hale, et al (46), of the Georgia Coastal Plain Experiment Station, have studied the effects of feeding a partially irradiated diet to dogs for a period of two years. This diet contains bacon at the level of 35% on a dry weight basis. The irradiated bacon (2.79 megarads, and 5.58 megarads) was stored at room temperature (10° to $33^{\circ}C$) for periods of six months to one year prior to feeding. No difference due to irradiation was found with respect to growth, weight maintenance, hemoglobin, packed cell volume, white blood cell counts, reproduction and lactation. At the termination of the experiment no pathologic

changes were found that could be attributed to feeding irradiated bacon. In the long term rat studies of Mead and Griffith (40), the irradiated bacon produced no detectable adverse effects as compared with the unirradiated control, except for a very slight and questionable decreased longevity. The Armed Forces Institute of Pathology has reviewed the histopathologic data from this study for the purpose of drawing tentative conclusions concerning the wholesomeness of irradiated bacon. No statistical workup has as yet been made and the tentative conclusion reached may be subject to change. However, the following provisional statement was made by the AFIP. "There does not appear to be any indication that the consumption of irradiated bacon (or fruit compote), by rats, produces histologic changes unequivocally attributable to the factor of food irradiation" (47). Dixon, et al (48), at the University of California in Los Angeles, fed the fat obtained from frying irradiated bacon (5.58 megarads) mixed into standard laboratory chow at the 10% level to two cancer-prone strains of mice for periods up to 741 days. During the experiment the percentage of fat mixed into the diet was boosted to 15% and later to 20%. The irradiated diet had no detrimental effects on the two strains of mice. The incidences of mammary cancer and hepatoma between controls, non-irradiated bacon-lipid, and irradiated bacon-lipid diet groups showed no significant differences. There were no significant differences in the incidences of other pathological changes among the diet groups. The rate of growth of animals in

the diet groups did not vary significantly. The rate of tumor growth and the weight of tumors were also similar between diet groups. The incidences of more than one tumor per animal and of pulmonary metastasis were not significantly different between diet groups. Schreiber and Nassett (49), at the University of Rochester, studied the absorption of lard and lean beef irradiated in a beam of accelerated electrons at six million rep. Test meals were fed to dogs using the various combinations of irradiated and non-irradiated lard and meat. Irradiated lard, whether fed by itself or with meat, was retained in the stomach to a greater extent than normal lard (65% versus 49%), filled the small intestine to a smaller extent (9% versus 13%) and was less readily absorbed (25% versus 38%) in a specified time. The peroxide value of lard rose abruptly on irradiation from 1-2 to 176 and, in 14 months of cold storage, continued to rise to over twice this value. It was concluded that irradiation of lard was detrimental so far as its digestion by the dog is concerned. Monty (50), John Hopkins University, obtained data demonstrating that carbonyl compounds of the types formed in irradiated food inhibited pancreatic lipase *in vivo* and *in vitro*, probably through their surface active properties. In rats, these carbonyl compounds were shown to depress the rate of absorption of lipid from the intestinal tract. Nevertheless, even though the rate of fat absorption was impaired, the net amount of absorption was not. It further appeared that the carbonyl compounds were themselves absorbed

and metabolized to a significant degree. In experiments lasting up to 4 weeks in female rats, the forced feeding of large amounts of aliphatic aldehydes and ketones (carbonyls) produced no recognized adverse effects. Attempts to find evidence for accumulation of the fed carbonyl compounds within the carcass were unsuccessful even though the analytical techniques were of a high order of sensitivity. Nevertheless, low O_2 and low temperature irradiation processing should continue to receive study, in an effort to reduce carbonyl formation, especially peroxides, to as low a level as possible.

The U. S. Army Medical Research and Nutrition Laboratory (51) conducted a two year, four generation study in rats fed a composite diet of nine foods: ground beef, cereal bar, fresh ham, peaches, powdered milk, haddock filets, bacon, beets, and green beans. This diet was supplemented with both vitamins and minerals. The food irradiation level was 5.58 megarads. In contrast to the one- and two-food studies mentioned above, in this study the irradiated foods were stored frozen, after irradiation, until incorporated into the diets. No toxic effects were observed in the study.

In addition to the histopathological examination of tissues of animals in the long term feeding experiments conducted locally by pathologists associated with each investigating group, the necropsy reports and a complete set of tissue sections obtained,

and blocks of paraffin-embedded tissues, are forwarded to the Armed Forces Institute of Pathology in Washington, D.C. for review and compilation of a separate over-all report. As of September 1961, approximately 90% of the total material anticipated has been received by the Armed Forces Institute of Pathology. Review of the histopathology found in studies of bacon, cabbage, codfish, sweet potatoes, green beans, fruit compote, beef, flour, shrimp, and carrots, fed to dogs, has been completed and individual preliminary reports are available. No evidence has been noted from these reviews to suggest that irradiation of the food produced any histopathologic changes. Although individual reports will continue to be prepared as the material is reviewed, the final summary report for each species should permit more meaningful conclusions as to the role, if any, of the irradiation of the various foods in the histopathology observed. These studies should be concluded and a final report anticipated near the end of 1962.

In addition to all of these "long term" experiments there have been several special studies (table 5) designated as studies of carcinogenicity. (Of course, the long term studies in rats also will have yielded data on potential carcinogenicity). Kline and Teply (52), Wisconsin Alumni Research Foundation, irradiated fresh pork-brain and egg, commercial sterol concentrates high in cholesterol and ergosterol, a mixture of vegetable oils, a mixture of ground meat-fish-cheese-milk powder, and lard. The irradiation

levels ranged approximately from 1/10 to 10 megarads. Non-irradiated materials were used as controls. In the studies utilizing 400 rats the lard was injected and the other materials were fed. In studies using a total of 3700 mice, lard was injected, the sterols and vegetable oils were fed, "painted" and injected, brain and egg were fed, and an alcohol-ether-soluble extract of the brain and egg and of the meat-fish-cheese-milk mixture was "painted" on the skin. The investigators concluded that no carcinogen could be demonstrated in the irradiated food preparations. Carcinogenicity studies by McKee and Zeldis (48) have already been described in connection with the discussion of the long term feeding studies with bacon, with no carcinogenicity being demonstrated. Calandra and Kay (20) have fed a composite test diet composed of six irradiated foods (codfish, green beans, chicken stew, beef stew, and peaches irradiated at 6 megarads and flour irradiated at 80,000 rep) to two cancer-susceptible strains of mice. The studies are still continuing. While preliminary results do not suggest any carcinogenicity in the irradiated food, no firm conclusions have yet been reached. Deichmann (53) is conducting a carcinogenicity study in four strains of mice fed a composite irradiated diet (5.58 megarads) composed of beef, tuna, corn, sweet potatoes and fruit compote. Feeding and gross pathology studies have been completed for approximately the first half of ten replicates. This preliminary data has not revealed any carcinogenicity. It is reasonable to expect that the full study will be

completed within approximately one year.

In 1957 Monsen (54) of the University of Illinois, College of Medicine, initiated a study to determine the carcinogenic effect, if any, of a composite diet composed of pork, chicken, evaporated milk, potatoes and carrots on two strains of mice. In 1958 he observed that a large number of his animals were becoming ill. Upon their sacrifice it was noted that a number of these animals had developed a peculiar cardiac lesion consisting of a dilatation of the left auricular appendage, which sometimes ruptured. The condition appeared at that time to represent a new disease. Since 1958 he has observed no new cases occurring in the animals on the study until about 600 days on the test. The original lesion had occurred after an average of only 85 days on the diet. At 600 days on diet he noted that, of the total number of experimental animals, nearly 50% of one strain on the irradiated diet had such lesions as compared to a much lower incidence among the controls. While attempting to investigate this finding he fed other mice irradiated or non-irradiated milk and was able to reproduce the lesion with either diet. It was then decided to repeat the experiment to study this particular lesion, since Monsen's original project was a carcinogenicity study such that the test animals could not very well be sacrificed at varying stages of the diet. The repeat study (table 6) has been set up and is underway in our Laboratory, the U. S. Army Medical Research and Nutrition Laboratory, Denver, Colorado, under the

direction of Lt. Colonel Thompson, VC, Chief, Pathology Division. Approximately 6,000 mice of the same strains (Cb and strong A) are involved in the feeding program. This study is divided into four phases: I. Breeding of the required strains of mice, II. A repeat of Monsen's original protocol, III. Pathogenesis and IV. Etiology. The breeding of the required number of mice has been completed and this phase of the project has been discontinued. All breeding stock whose offspring were placed in the other phases of the experiment are being allowed to live out their life span. These mice will receive a complete necropsy at the time of their death, and will receive histopathological examination of all tissues. In Phase II, all mice of both strains have been started on feed. These mice are divided into three groups of paired litter mates for each strain and are being fed, respectively, the composite irradiated diet, the non-irradiated control (with commercial vitamin and salt mixtures added to each diet), and a commercial laboratory rodent pellet diet as a second control. Sacrifices and complete histopathologic examinations are scheduled for 200, 300, 400, 500 and 600 days after being placed on the diets. All mice of this phase will be sacrificed by 30 June 1962. In Phase III small groups of mice fed only the irradiated diet (vitamin supplemented) have been sacrificed at 25 day intervals from the time they were started on the diet up to 400 days. The tissues of these animals are being subjected to extensive histopathological examination, including serial sectioning of the hearts

in an effort to describe early manifestations of the cardiac or other lesions which may develop. In Phase IV groups of mice are being fed one of 20 different diets. Each of the 5 basic composite diets (each containing one irradiated food item) is divided into four groups: cooked with vitamins, cooked without vitamins, uncooked with vitamins, and uncooked without vitamins. Sacrifices and histopathologic examinations are scheduled for 100, 200, 400, 500 and 600 days on feed. If a significant number of lesions are obtained this phase of the experiment should provide some information as to the responsible food factor. Since beginning this experiment several smaller additional experiments have been initiated. In one of these, the irradiated diet fed is similar to that in the major experiment with the exception that the milk component is stored at 10°F rather than at room temperature. In another, mice have been placed on a milk diet, fortified with vitamin mix, and divided into four groups depending upon whether the milk is cooked or uncooked and irradiated or non-irradiated. Since the heart lesion observed might be due to dietary stress associated with a genetic aspect, extensive records are being maintained as to the breeding program, and the animals on test are individually identified. This experiment has not progressed sufficiently far to permit any firm conclusions as to the role of irradiated food in the production of the heart lesion. In the total group very few heart lesions have been observed to date but studies have not reached the age groups at

which Monsen (54) observed the largest proportion of affected animals. Our experiment should be completed in the Autumn of 1962. It should be emphasized that while this experiment should yield valuable information concerning carcinogenicity, the heart lesion observed by Monsen appears to be a degenerative lesion, and is definitely not tumor.

Potential mutagenic effects (through chemical changes created in food by irradiation) can receive partial study in the four generation rat tests and in the mouse experiments, but further study needs to be given to methods for assessing this possible threat.

Several investigators have studied blood and tissue enzymes in animals fed control and irradiated foods in an attempt to describe early differences at the chemical level possibly indicative or predictive of lesions due to the irradiation of the diet. Changes in duodenal and intestinal transaminases, monoamine oxidase and sucrase in rats fed irradiated oranges or shrimp have already been mentioned. In the long term rat study conducted at the Army Medical Research and Nutrition Laboratory (51) in which the nine food composite irradiated diet was fed there were no differences between diet groups in the activities of liver xanthine oxidase, succinic dehydrogenase, alkaline phosphatase and serum alkaline phosphatase. However, the liver cytochrome oxidase activity was increased in male rats fed the irradiated foods. In studies

conducted by Tinsley (17), in comparison with non-irradiated pork, irradiated pork appeared to cause a decrease in fatty acid oxidation of kidney mitochondria, an increase in DPN-ATP-ase in liver mitochondria and an increase in cytochrome oxidase of liver mitochondria. The irradiated jam ration was associated with a decrease in fructose oxidation in heart homogenates (17). In serum and erythrocyte enzyme activity studies by Brin, et al (55), abnormalities in the enzyme level were primarily associated with vitamin deficiencies on unsupplemented irradiated food diets. While enzyme studies will no doubt yield extremely valuable basic information and should be continued, it seems to this reviewer that such studies must ultimately depend for interpretation upon feeding tests in the intact animal using the measurements which have been mentioned repeatedly, viz.: growth, longevity, reproductive ability, lactation, morbidity as revealed by the usual indices of disease, and studies of gross and microscopic pathology. To the extent that blood and tissue enzyme changes come to be relied upon as indices of disease will they be useful in forming judgments as to the safety of irradiated food. It seems likely that such judgments should and can be made reasonably well before the enzyme changes are reliably interpretable.

Under existing law the presence of any detectable residual radioactivity above background (radioactivity of non-irradiated foods) would preclude clearance by the Food and Drug Administration for human consumption (56). Problems center around the definition of

what constitutes detectable residual radioactivity and the exacting techniques necessary for accurate counting. Standard counting methods have been established and preliminary data on selected irradiated food items have been collected by Meneely, et al (57,1), at Vanderbilt University. Background radioactivity measurements were made using cans filled with triple distilled water and un-irradiated pork, ham, beef and chicken. The gamma ray spectra obtained from the un-irradiated food did not differ from the spectra of normal humans (1). Meneely reported that no induced radioactivity could be detected in raw pork irradiated by cobalt 60 or by 8 or 11.2 mev electrons. Induced radioactivity was found in raw pork irradiated by 12, 13, and 16 mev electrons. Studies on additional foods are in progress. The concensus of most authorities appears to be that induced radioactivity is not a problem providing fixed cobalt 60 or cesium 137 sources are used, or that the irradiation energy is kept below threshold levels for nuclear reactions (58,59).

Of all the studies conducted in the program, one of the most interesting and most productive of basic nutritional and biochemical data is that concerned with the hemorrhagic syndrome in rats fed irradiated beef first discovered by Metta and Johnson (60) of the University of Illinois. Various investigators have since found that rats fed non-irradiated beef may also develop hemorrhages, though less frequently. A hemorrhagic syndrome in rats can also be produced by feeding pork, cooked or uncooked, irradiated or

non-irradiated (61-64). These observations have led to exciting studies on the interrelationships between vitamin K, estrogens, vitamins A and E, and dietary amino acids (62, 64-68). The concensus of most investigators seems to be that the hemorrhage is primarily due to the irradiation destruction of vitamin K, and that adequate supplementation of the irradiated diet with vitamin K, or vitamin K containing foods, will go far to solve the problem. The U. S. Army has sponsored a great deal of research on the nutrient changes (as opposed to possible toxic changes) in food occasioned by irradiation processing. However, other speakers will discuss this (including effects on macro- as well as micro-nutrients) in more detail, and I will merely generalize, with respect to the vitamins, that vitamins A, E and K are particularly susceptible to destruction by irradiation and that thiamine, pyridoxine, and vitamin C are also likely to be reduced - as with heat processing (59, 69-71). However, it is felt that consumption of varied diets containing some non-irradiated foods and/or supplementation with individual vitamins will eliminate the problem.

In conclusion (table 7) it appears desirable to review the unfavorable findings that have been mentioned above:

1. The question of thyroiditis associated with feeding irradiated flour to dogs was raised by Reber, but the numbers were so small as to be easily due to chance. Should similar abnormalities

not be found in the rats studied by Tinsley and Bone, or in the mice being studied (in carcinogenicity experiments) by Calandra and Kay, this problem may be dismissed.

2. Irradiated whole oranges fed to rats, as studied by Phillips, was associated with a lower growth rate in third generation animals. So far as I know, this is not being studied further. Peeled oranges, irradiated before peeling, caused no detectible difficulties.

3. Mead and Griffith report that irradiated bacon and fruit compote appear to cause a slight decrease in longevity of rats. Further statistical evaluation of these data has been requested. If the decreased longevity is confirmed, and is of a magnitude to be biologically significant, then the problem certainly deserves further study.

4. Decreased rates of digestibility of fats does not necessarily imply toxicity, and should be of little importance so long as net digestibility is not decreased.

5. The finding of increased spleen weights by Larson in dogs fed fruit compote (and to a less extent in dogs fed green beans) does not seem of biological significance. In the dog the spleen may change weight rapidly, in minutes, through a change in blood content. It will be worthwhile to review the sections of spleen to see if differences in blood content might suggest this explanation for the varying spleen weights.

6. Tinsley found that rats raised on the irradiated carrot rations had a lower rate of growth than the controls, and this effect was more pronounced in the males. However, there was no difference in growth rate between animals on the two levels of irradiation. Control animals had a considerably higher concentration of vitamin A in the liver. The growth depressing effect may be related and may be due to changes in the isomeric form of carotenes in the diet caused by irradiation. Studies to re-evaluate this problem have been started.

7. Poor reproductive performance in dogs seems now to have been due to vitamin E deficiency. Repeat studies that should provide answers will be completed in one, and in two years from now.

8. The degenerative heart lesions appearing in mice at an early age, discovered by Monsen and apparently accelerated by the irradiated diet have not been successfully duplicated as yet. However, no statement can be made yet concerning these lesions appearing later in life. The study at U. S. Army Medical Research and Nutrition Laboratory by Lt. Colonel Thompson represents a very painstaking, comprehensive and detailed pathological study of this problem which should yield answers in one more year.

One, or at the most, two more years should see completion of the histopathology review of the long term feeding experiments, the repeat studies cited, and the carcinogenicity studies in mice.

At that time, if results appear favorable, we may be able to proceed with "long term" (4-6 months') feeding tests in volunteer human subjects at our Laboratory in Denver, Colorado. Short term (15 day) toxicity studies have been conducted there in humans (8), in the past, but no human feeding studies have been carried out since 1958. No abnormalities were found, which is not surprising in such short tests. It is, of course, questionable whether studies of 4-6 months' duration in humans will be long enough to expect potential abnormalities to appear. However, longer (than 6 months') tests will not be necessary for making reasonable judgments of wholesomeness based on the accumulated animal and human data that should then be available.

This program has been reviewed by the Surgeon General's Advisory Committee on Nutrition who stated that those adverse effects associated with ingestion of irradiated foods "which have been explored to a point of firm interpretation are all explicable on the grounds of nutrient alteration such as occurs in other processing procedures. Continuation of the planned investigations and initiation of additional studies of certain of the less clear phenomena are desirable" (58b).

Such investigations are now being carried out in the Surgeon General's Study on the Wholesomeness of Irradiated Foods.

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TABLE I.

RADIATION PROCESSED FOOD

LONG TERM FEEDING STUDIES

	INVESTIGATOR	RADIATION KILORADS	ANIMAL	RESULTS
POTATOES	BROWNELL, MICHIGAN	13 - 20 27 - 40	RATS	SLIGHT ↑ MORTALITY 1st & 2nd GENERATION
	KLINE, WISC. ALUM. RES	7.5 - 8.5 15 - 17	RATS	NEGATIVE
	McCAY, CORNELL	7 15	DOGS	NEGATIVE
FLOUR	BUBL, TINSLEY OREGON STATE	37 74	RATS	NEGATIVE
	REBER, U. OF ILLINOIS	37 74	DOGS	NEGATIVE (? THYROIDITIS)
ORANGES	PHILLIPS, SYRACUSE	140 280	RATS	(PEELED) NEGATIVE (WHOLE) ↓ GROWTH
	BLOOD, VANDERBILT	140 280	MONKEYS	NEGATIVE

TABLE 2

RADIATION PROCESSED FOOD

LONG TERM FEEDING STUDIES

2.79 & 5.58 MRADS

INVESTIGATOR	ANIMAL	RESULTS
BEEF:		
BLOOD, VANDERBILT	RATS	NEGATIVE
Mc CAY, CORNELL	DOGS	√ FERTILITY ? VIT. E
Mc CAY, CORNELL	DOGS (5.58 MRADS)	EXPERIMENT INCOMPLETE
REBER, U. of ILLINOIS	DOGS	NEGATIVE
CLARKSON, BOWMAN – GRAY	DOGS (5.58 MRADS)	EXPERIMENT INCOMPLETE
BEEF STEW:		
DEICHMAN, U. of MIAMI	RATS	NEGATIVE
PORK:		
TINSLEY, OREGON STATE	RATS	NEGATIVE
Mc CAY, CORNELL	DOGS	NEGATIVE
CHICKEN:		
BLOOD, VANDERBILT	DOGS	NEGATIVE
RICHARDSON, TEXAS AG. EXPT. STA.	RATS	NEGATIVE
CHICKEN STEW:		
PHILLIPS, SYRACUSE	RATS	NEGATIVE
Mc CAY, CORNELL	DOGS	NEGATIVE
CODFISH:		
SALMON & NEWBERNE, AUBURN	RATS	NEGATIVE
" "	DOGS	NEGATIVE
TUNAFISH:		
McCAY, CORNELL	DOGS	NEGATIVE
PAYNTER, HAZLETON LABS	RATS	NEGATIVE
SHRIMP:		
PHILLIPS, SYRACUSE	RATS	NEGATIVE
ENGEL, VA POLYTECH INST	DOGS	NEGATIVE

TABLE 3

RADIATION PROCESSED FOOD

LONG TERM FEEDING STUDIES

2.79 & 5.58 MRADS

INVESTIGATOR	ANIMAL	RESULTS
PEACHES:		
BLOOD, VANDERBILT	MONKEYS	NEGATIVE BUT VIT. C NEEDED
TINSLEY, OREGON STATE	RATS	NEGATIVE
FRUIT COMPOTE:		
MEAD U.C.L.A	RATS	NEGATIVE (? $\downarrow$ LONGEVITY)
LARSON, MED COLLEGE OF VA.	DOGS	$\uparrow$ SPLEEN WEIGHTS
PINEAPPLE JAM:		
BLOOD, VANDERBILT	DOGS	GLYCOSURIA
TINSLEY, OREGON STATE	RATS	NEGATIVE
DRIED WHOLE EGG:		
PROCTOR, MASS INST TECH	DOGS	POOR FERTILITY
EVAPORATED MILK:		
DEICHMAN, U. of MIAMI	RATS	NEGATIVE
"	DOGS	NEGATIVE

TABLE 4

RADIATION PROCESSED FOOD

LONG TERM FEEDING STUDIES

2.79 & 5.58 MRADS

INVESTIGATOR	ANIMAL	RESULTS
CARROTS:		
ENGEL, VA POLYTECH INST	DOGS	NEGATIVE
TINSLEY, OREGON STATE	RATS	↓ GROWTH
GREEN BEANS:		
RICHARDSON, TEXAS AG EXPT STA	RATS	NEGATIVE
LARSON, MED COLLEGE OF VA	DOGS	↑ SPLEEN WEIGHTS
CABBAGE:		
HALE, GA COSTAL PLAIN EXPT STA	DOGS	NEGATIVE
PHILLIPS, SYRACUSE	RATS	NEGATIVE
CORN:		
McCAY, CORNELL	DOGS	NEGATIVE
PAYNTER, HAZLETON LABS	RATS	NEGATIVE
SWEET POTATOES		
SALMON & NEWBERNE, AUBURN	RATS	NEGATIVE
" "	DOGS	NEGATIVE
BACON:		
HALE, GEORGIA C.P. EXP. STA	DOGS	NEGATIVE
MEAD, U. C. L. A.	RATS	NEGATIVE (? ↓ LONGEVITY)
BACON LIPID:		
McKEE, U. C. L. A.	MICE	NEGATIVE IN CARCINOGENICITY STUDY
LARD:		
NASSET, ROCHESTER	DOGS	↓ RATE OF DIGESTION

TABLE 5

RADIATION PROCESSED FOOD

CARCINOGENICITY STUDIES

INVESTIGATOR	FOODS	ANIMALS	RESULTS
1. (AS MENTIONED IN PREVIOUS SLIDES)		RATS	NEGATIVE
2. KLINE & TEPLEY, WISC. ALUM RES FOUND	PORK BRAIN & EGG STEROL CONCENTR. VEGETABLE OILS GROUND MEAT FISH, CHEESE MILK, LARD	MICE RATS	NEGATIVE
3. McKEE & ZELDIS UCLA	BACON LIPIDS	MICE	NEGATIVE
4. CALANDRA & KAY, IND BIO-TEST LABS	CODFISH GREEN BEANS CHICKEN STEW BEEF STEW PEACHES, FLOUR	MICE	UNFINISHED BUT NEGATIVE TO DATE
5. DEICHMANN, U of MIAMI	BEEF, CORN TUNA FISH SWEET POTATOES FRUIT COMPOTE	MICE	UNFINISHED BUT NEGATIVE TO DATE

TABLE 6

DEGENERATIVE HEART LESION IN MICE

(MONSEN, U. of ILLINOIS, DESCRIBED IN 2 STRAINS OF MICE)

COMPOSITE DIET: PORK, CHICKEN, EVAPORATED MILK, POTATOES, CARROTS

USAMRNL - STUDY REPEATED AND EXTENDED - 1960-1962:

PHASE I BREEDING OF ALL EXPERIMENTAL ANIMALS - PARENT GENERATION LIVE OUT LIFE SPAN. GENETIC RECORDS KEPT

PHASE II REPEAT OF MONSEN'S EXPERIMENT - WITH 2 CONTROL GROUPS SACRIFICE OF ANIMALS AT 200, 300, 400, 500, 600 DAYS

PHASE III PATHOGENESIS STUDY - ANOTHER GROUP, FED ONLY IRRADIATED COMPOSITE; SACRIFICES AT 25 DAY INTERVALS UP TO 400 DAYS ON DIET

PHASE IV ETIOLOGY STUDY - a) 20 DIETS: ONE OUT OF 5 ITEMS IRRADIATED IN EACH, DIVIDED AS TO WHETHER DIET IS COOKED, UNCOOKED, WITH VITAMIN AND WITHOUT VITAMIN SUPPLEMENT b) MILK - STORAGE TEMPERATURE VARIED c) MILK DIET ALONE

TABLE 7

RADIATION PROCESSED FOOD

REVIEW OF REMAINING UNFAVORABLE FINDINGS

IRRADIATED FOOD	ANIMAL	OBSERVATION	INVESTIGATOR
1. FLOUR	DOGS	THYROIDITIS (SMALL NUMBER)	REBER
2. WHOLE ORANGES	RATS	↓ GROWTH, 3rd GENERATION	PHILLIPS
3. BACON AND FRUIT COMPOTE	RATS	? ↓ LONGEVITY	MEAD
4. FATS (LARD)	DOGS	↓ RATE OF DIGESTION	NASSET
5. FRUIT COMPOTE (& GREEN BEANS)	DOGS	↑ SPLEEN WEIGHTS	LARSON
6. CARROTS	RATS	↓ GROWTH RATE	TINSLEY
7. BEEF	DOGS	↓ FERTILITY	McCAY
8. COMPOSITE DIET	MICE	HEART DEGEN. LESION	MONSEN

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